

Systems Biology in a Computational Toxicology Framework

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Systems Biology

- Quantitative evaluation, through both laboratory experiments and computer simulation, of the manner in which the components of biological organisms are organized together to maintain normal physiological function. These components include:

Molecules, Signaling Motifs, Organelles,
Cells, Organs, Organisms & Populations

Systems Biology & The CIIT-CHR Core Research Program

- **Background** – The Issues
- **Approaches** – The New Tool Box
- **Integration** – Directions at CIIT-CHR
- **Rewards** – Value of a 'Systems' Approach

The Same, Old Questions

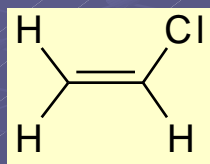
- What environmental stressors (chemicals) may adversely affect human health?
- At what levels are these stressors likely to have significant health effects?
- What determines the sensitivity of individuals to these stressors – lifestyle, genetics, etc.?
- What public health measures are required to insure the absence of morbidity and mortality from these stressors in specific populations?

The Environmental Health Tool Box – 1996

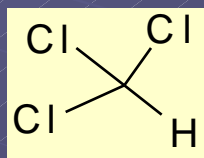
- **Mechanistic Studies** – establish mode of action, infer shape of D-R curve, and define 'effective' tissue dose
- **Physiologically Based Dosimetry Models** – permit extrapolations of tissue dose for a variety of exposure conditions
- **Biologically Based Dose Response (BBDR) Models** – permit evaluation of level of risk in relation to tissue dose based on biological principles

Mode of Action – Some Examples

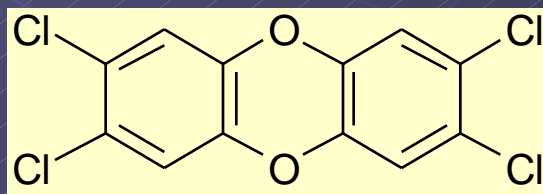
- DNA Reactivity & Mutagenesis – Vinyl Chloride



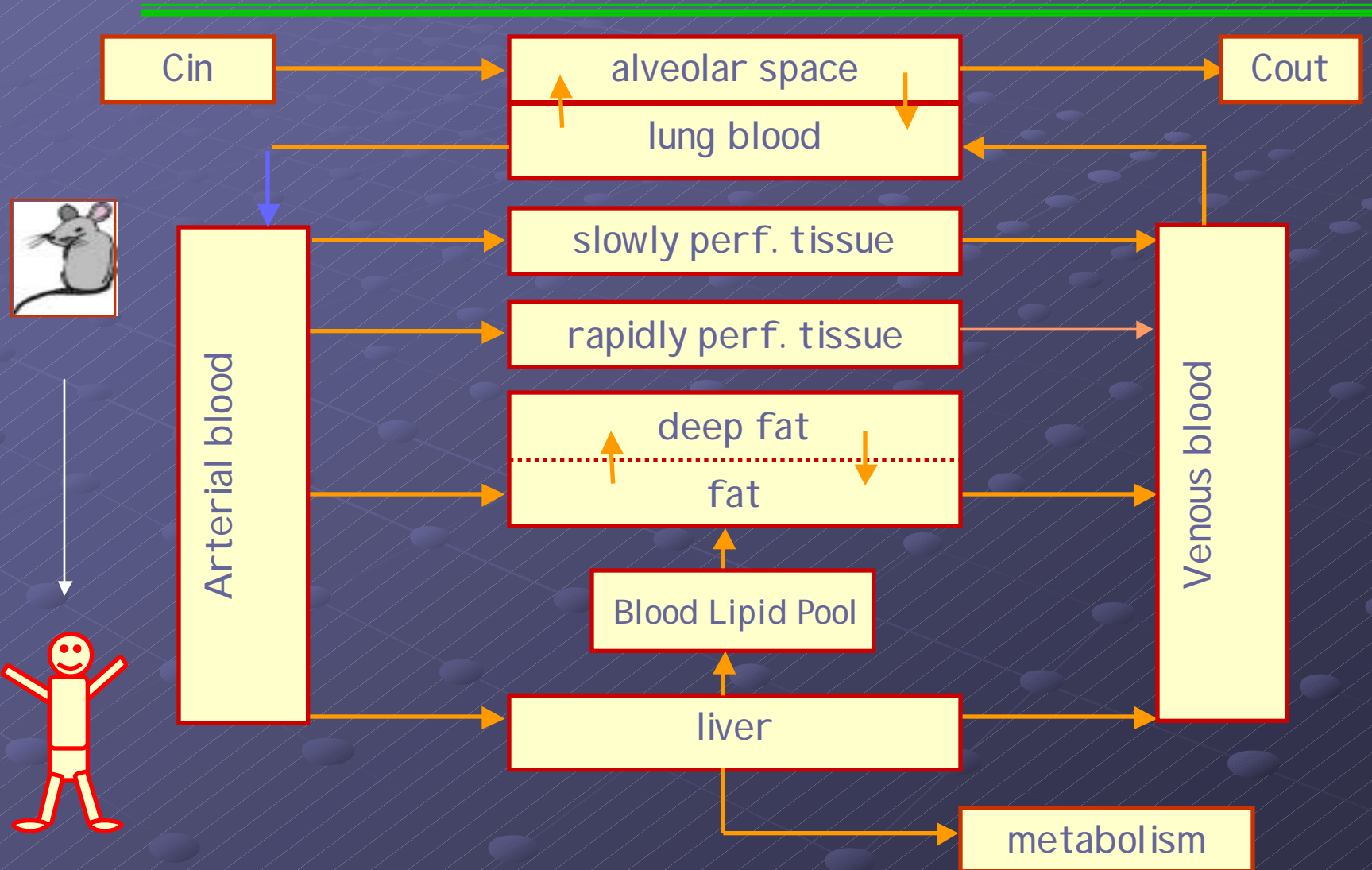
- Cytotoxicity and Hyperplasia – Chloroform



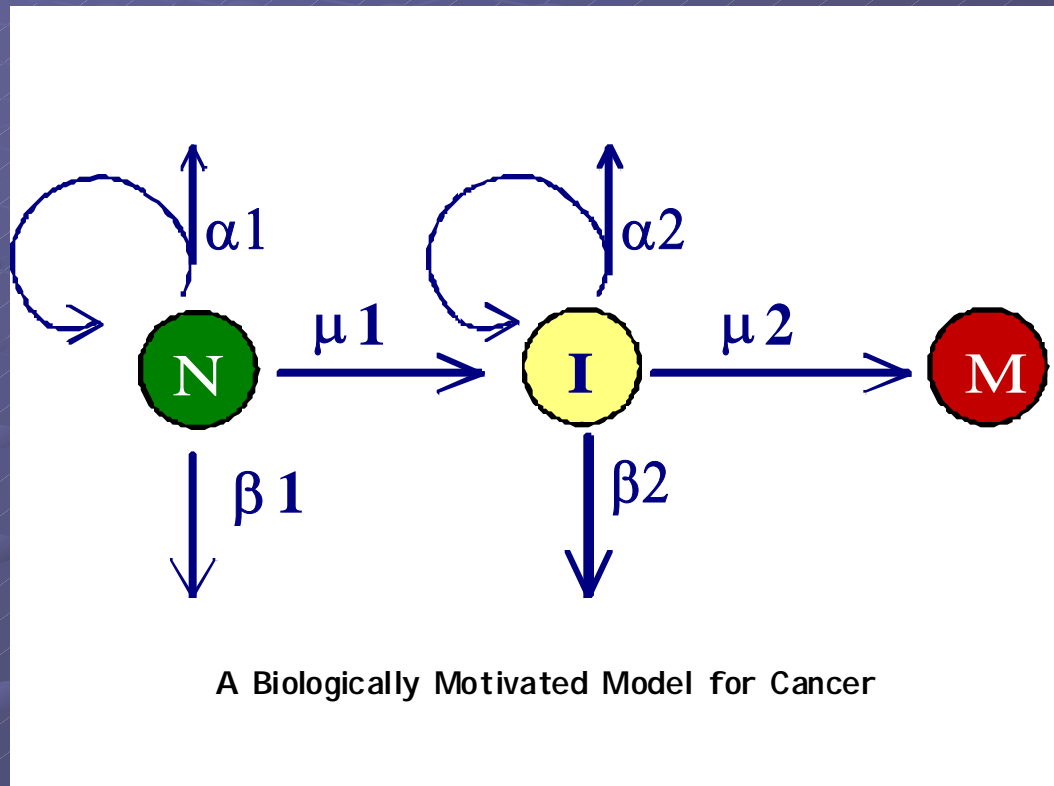
- Receptor Binding & Transcriptional Activation – e.g., TCDD, Endocrine Active Compounds (Anti-Androgens, Estrogenic compounds, etc.)



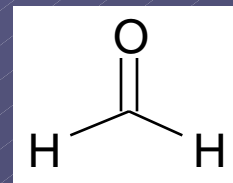
Simulation Models that Predict Tissue Dose



Biologically Based Dose Response Models



Capture dose-dependencies of main processes
although lacking in specific biological detail in
pathways



CIIT-CHR

Formaldehyde Risk Assessment

- Toxicity studies find nasal toxicity & cancer
- Mechanistic studies establish regional distribution of DNA-cross links, cytotoxicity
- Fluid dynamics models predict airflow patterns and regional dosimetry in nasal tissues
- Risk Assessments integrate dosimetry and response data into the two stage cancer model

Now, we are discovering the biological parts list

- Genomics
- Transcriptomics
- Proteomics
- Metabonomics

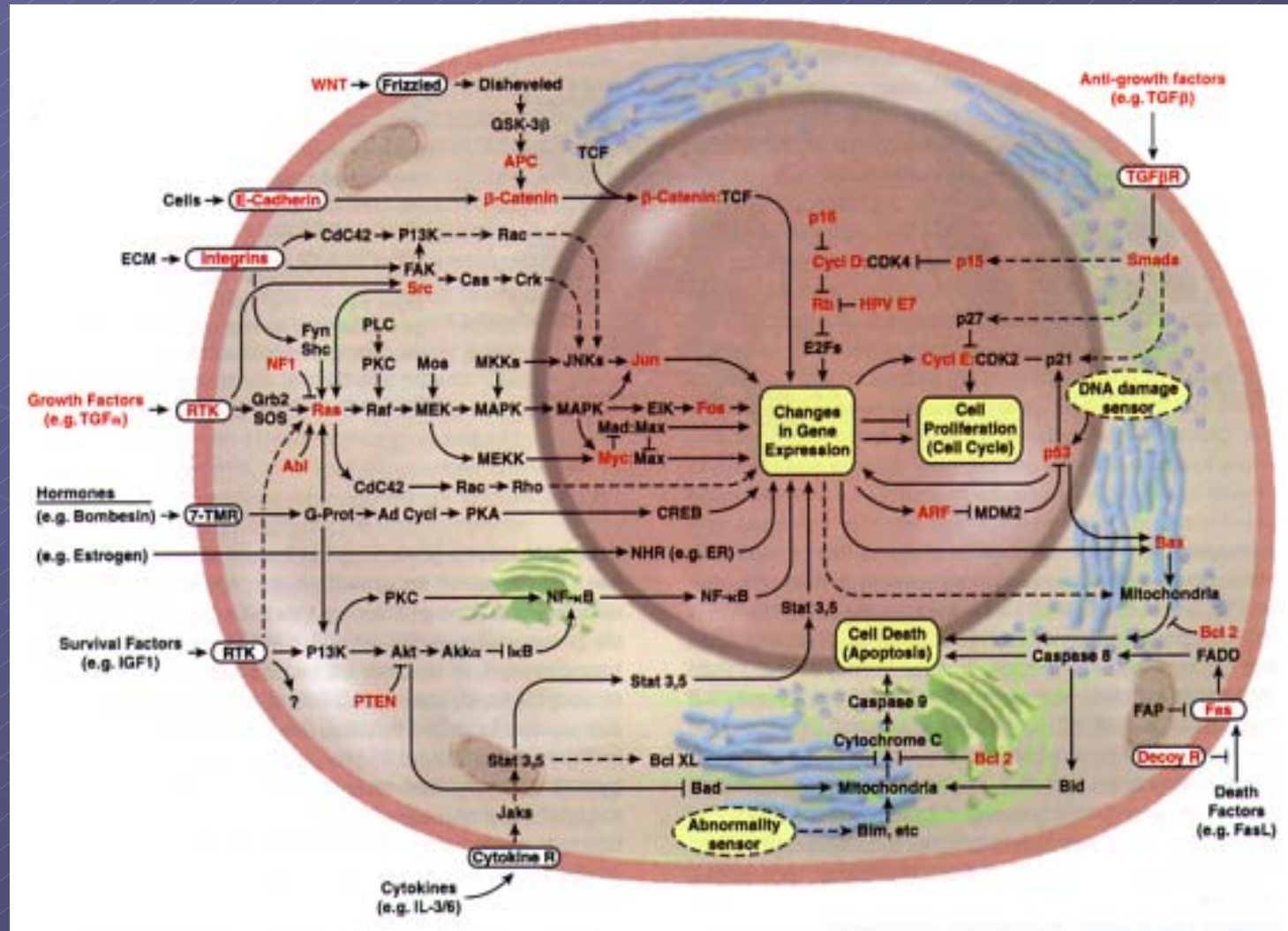
And trying discover how to use them in biology and risk assessment

A Post-Genomic World View

- Reconstruct molecular circuitry
- Map out protein networks that determine the logic of cellular functions, including responses to physiologic ("read also toxicological") stresses
- Create mathematical models of these biological circuits and predict biological responses of cells

¹ Lander and Weinberg, Journey to the Center of Biology, Science, 287, 1777-1782

Molecular Circuitry



Hanahan and Weinberg, Hallmarks of Cancer, Cell, 100, 57-70, 2000.

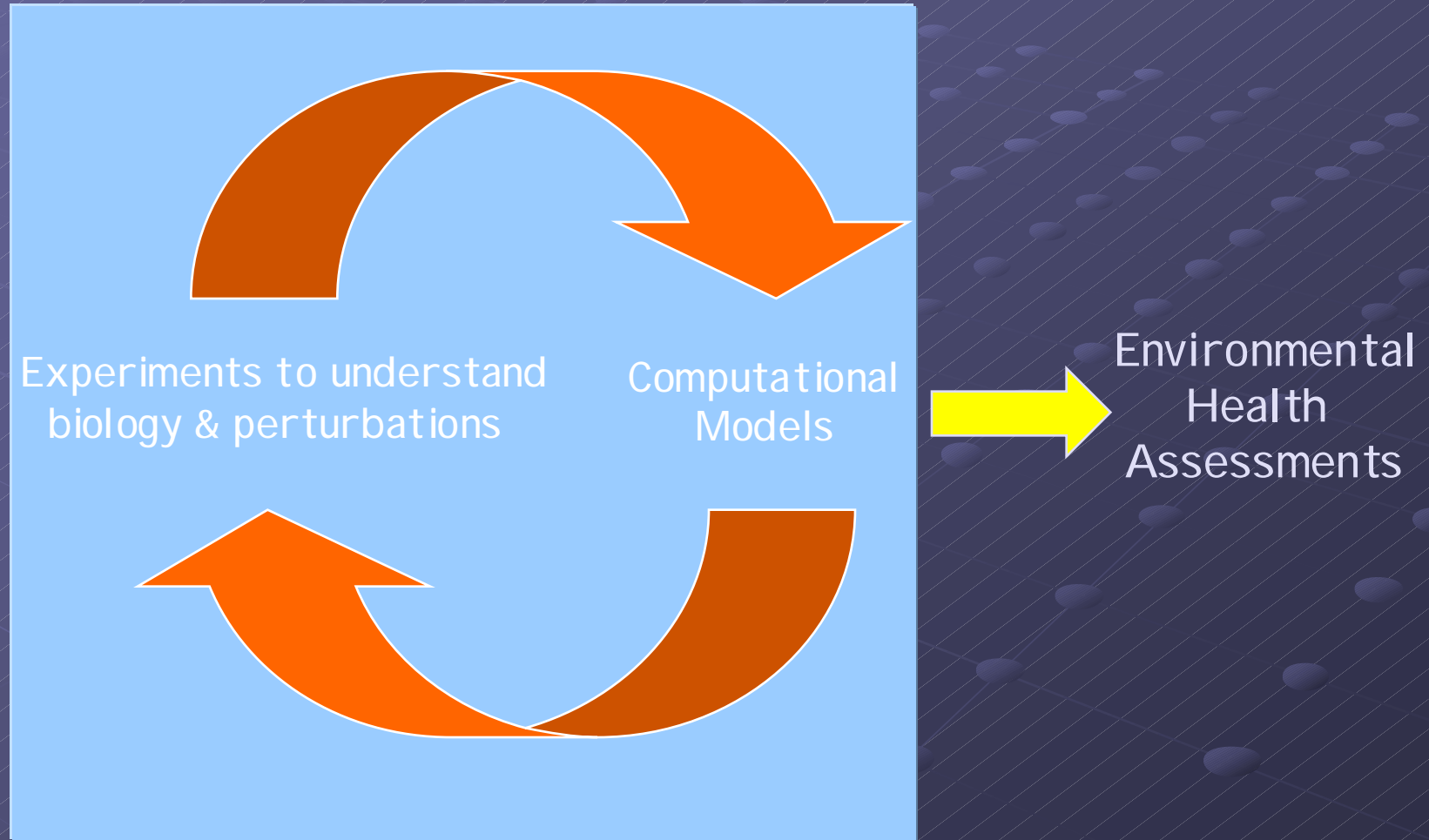
What are we trying to achieve?

- 1) Unravel the manner in which this circuitry is organized from a molecular to organism level to maintain normal function – **i.e., the biology**
- 2) And, the manner in which chemicals and genetics act to impair their function and cause adverse health consequences – **i.e., the perturbations**

Systems Biology

- Systems biology unravels the quantitative relationships between the content, structure and dynamics of biological organisms
- Characterization of these relationships requires interdisciplinary co-operation using both experimental and computational approaches at different levels of biological organization

Systems Biology and Environmental Health

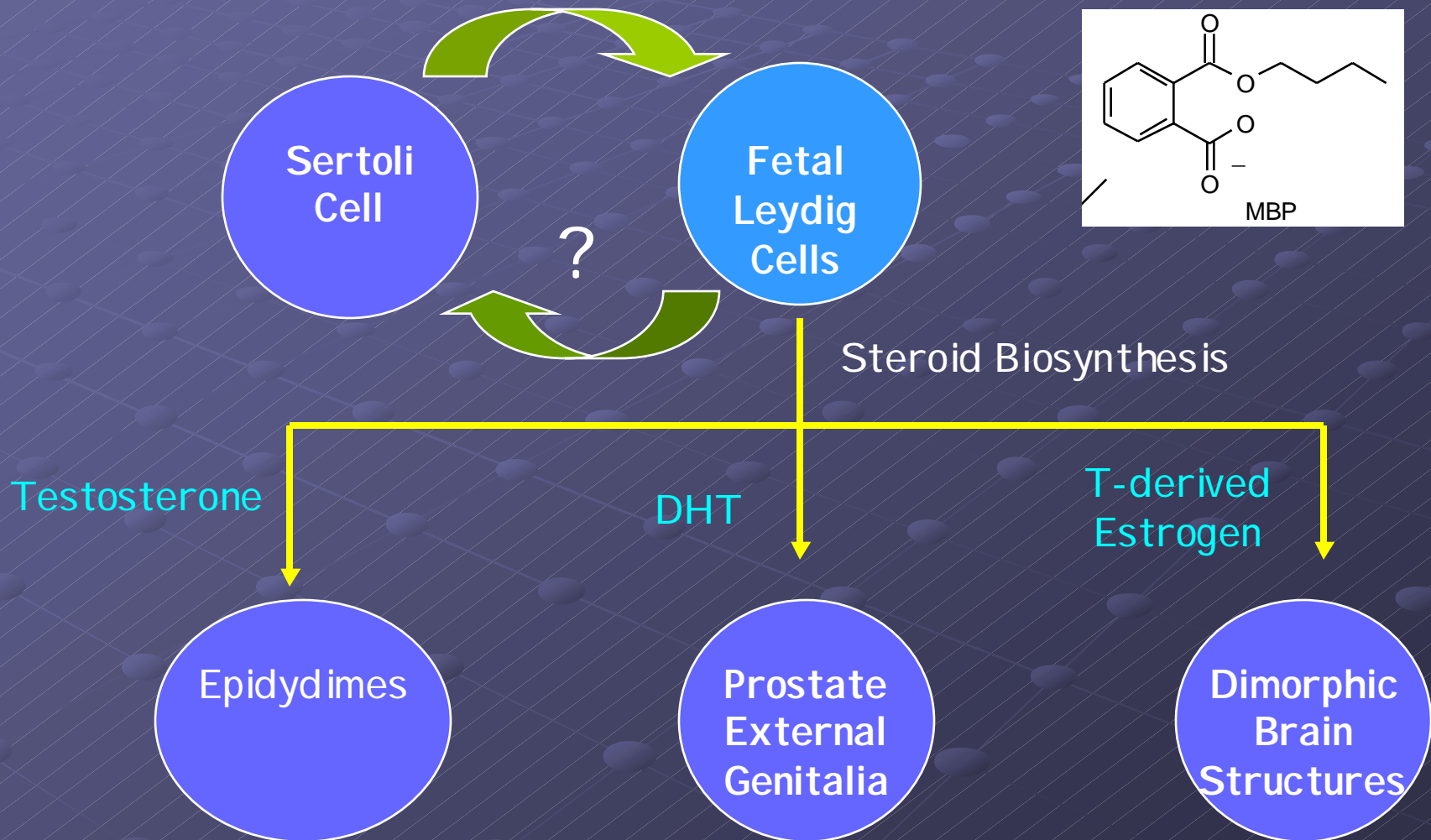


Systems Biology & Environmental Health

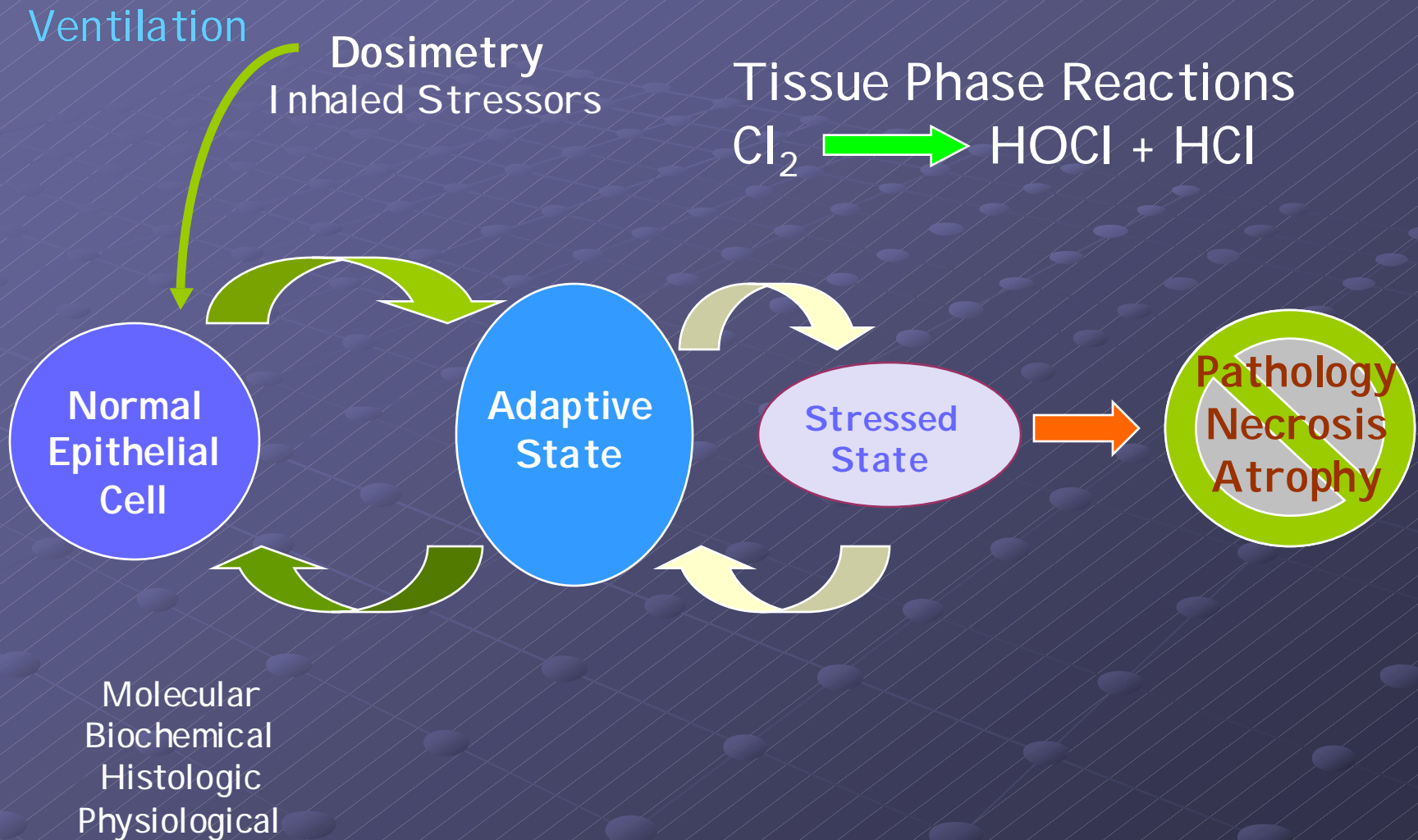
- Environmental Health Assessments grounded in knowledge/discoveries in **molecular and cell biology**
- Dosimetry and BBDR models developed/tested for the normal signaling circuitry and endogenous processes and extended to account for **perturbations** by exogenous compounds
- **Dose Response assessments** predicting when perturbations become large enough to produce adverse consequences

Reproductive/Developmental Biology

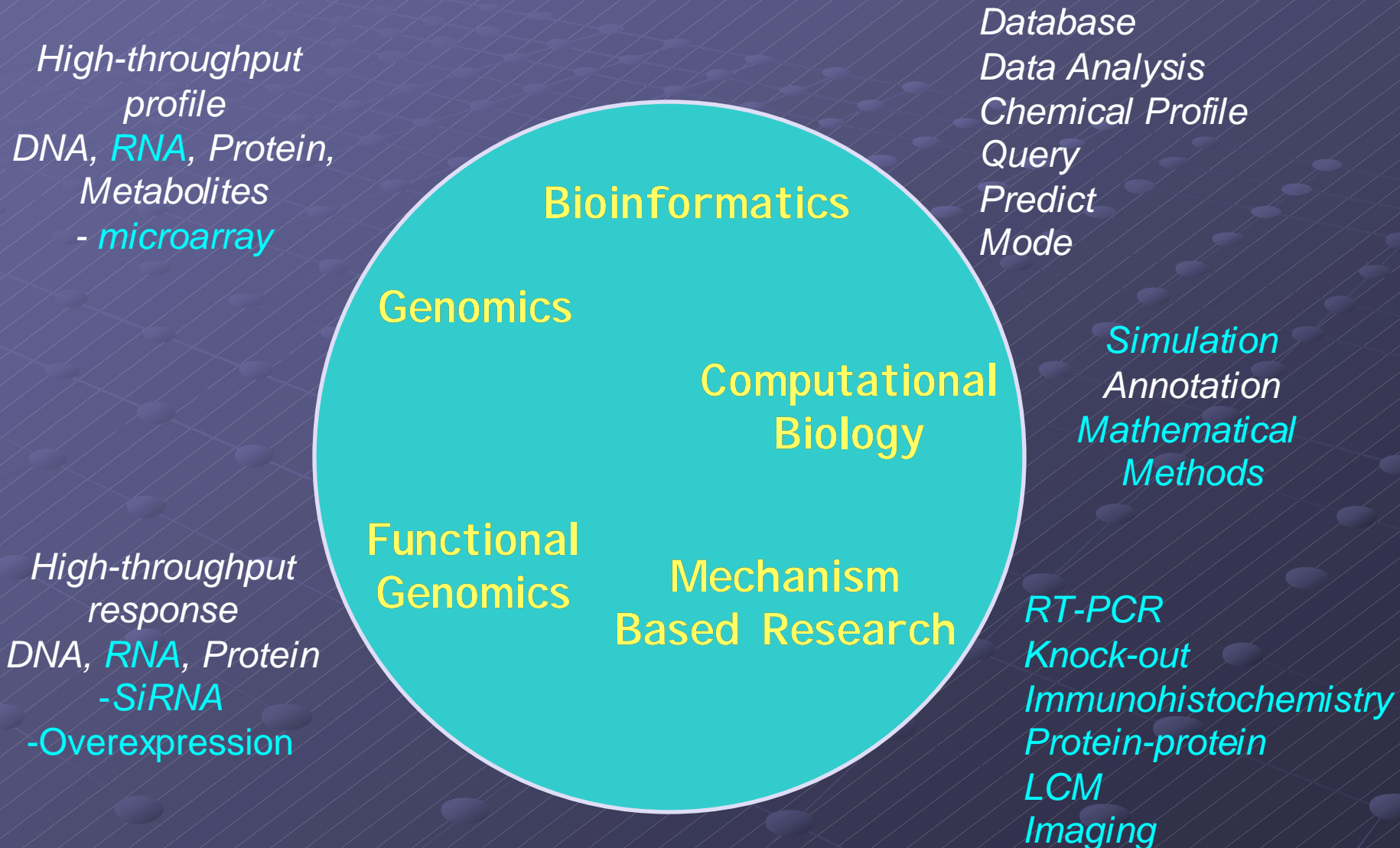
Anti-androgens



Respiratory Biology



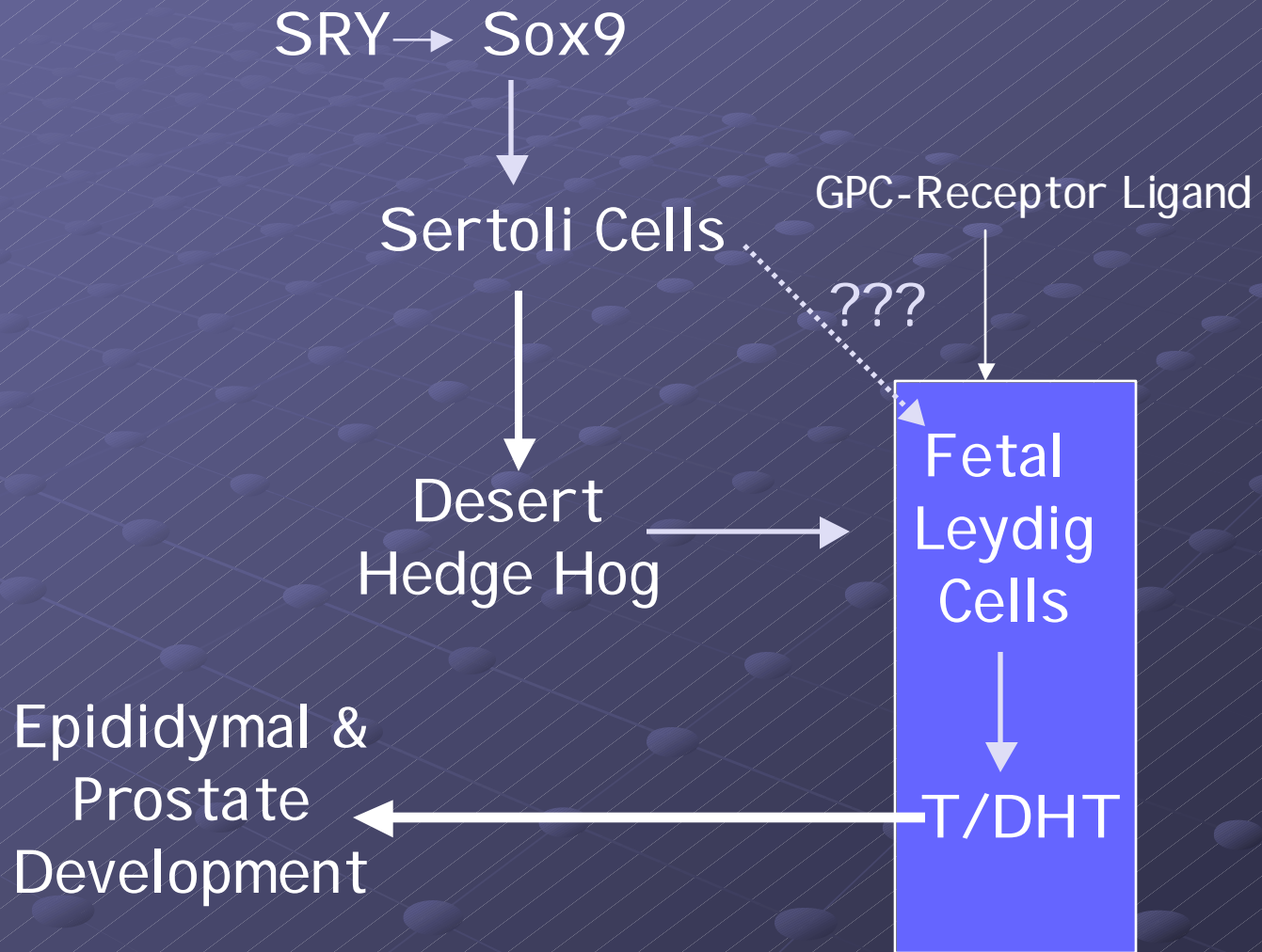
Systems Biology Toolbox



High Throughput, High Coverage Genomics

- Evaluate 'all' potential targets
- Establish time & dose responses
- Avoid 'blinders'
- Keep 'hypotheses' flexible
- Capture causes and consequences

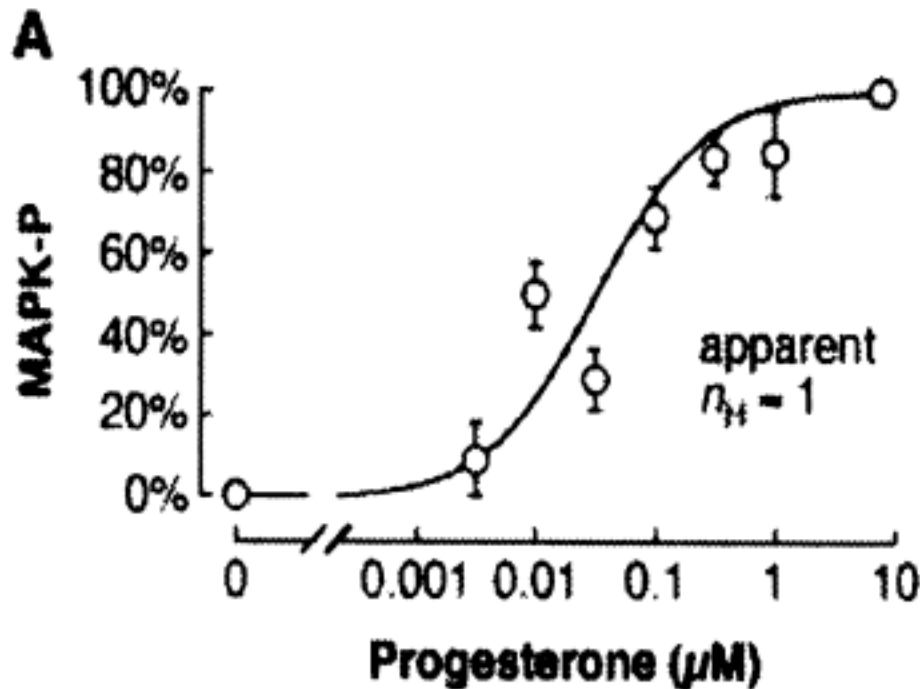
High Throughput, High Coverage Genomics



Functional Genomics

- Establish affected networks/circuits
- Tease out causes from consequences
- Develop refined hypothesis
- Co-ordinate with quantitative simulation of hypotheses

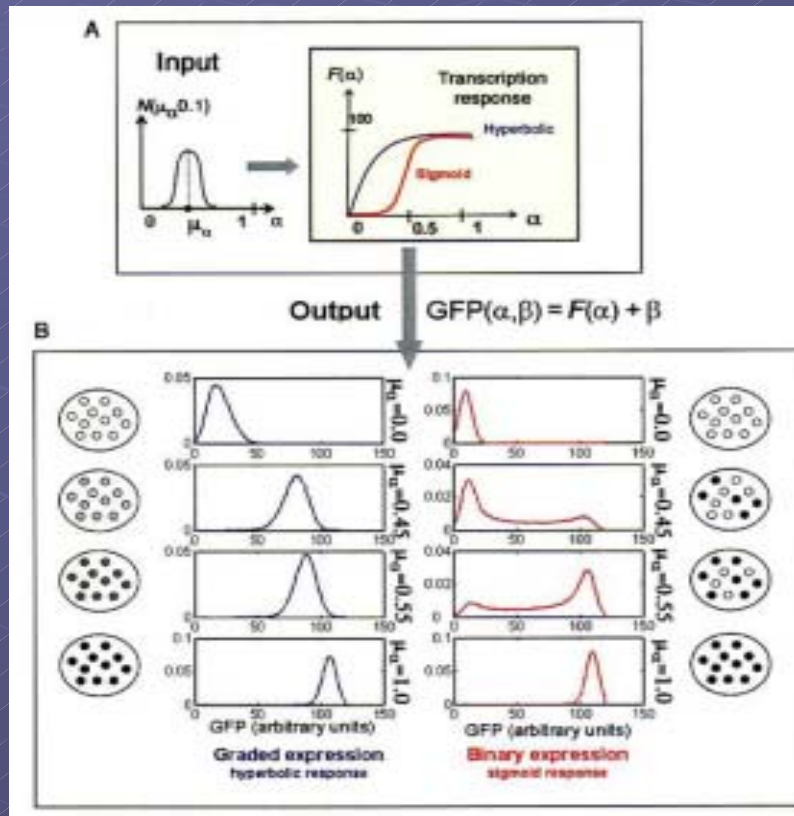
Evaluating Molecular Circuits



- Maturation mediated by progesterone is associated with MAP kinase activation.

Machleder and Ferrell, Science, 280, 895.

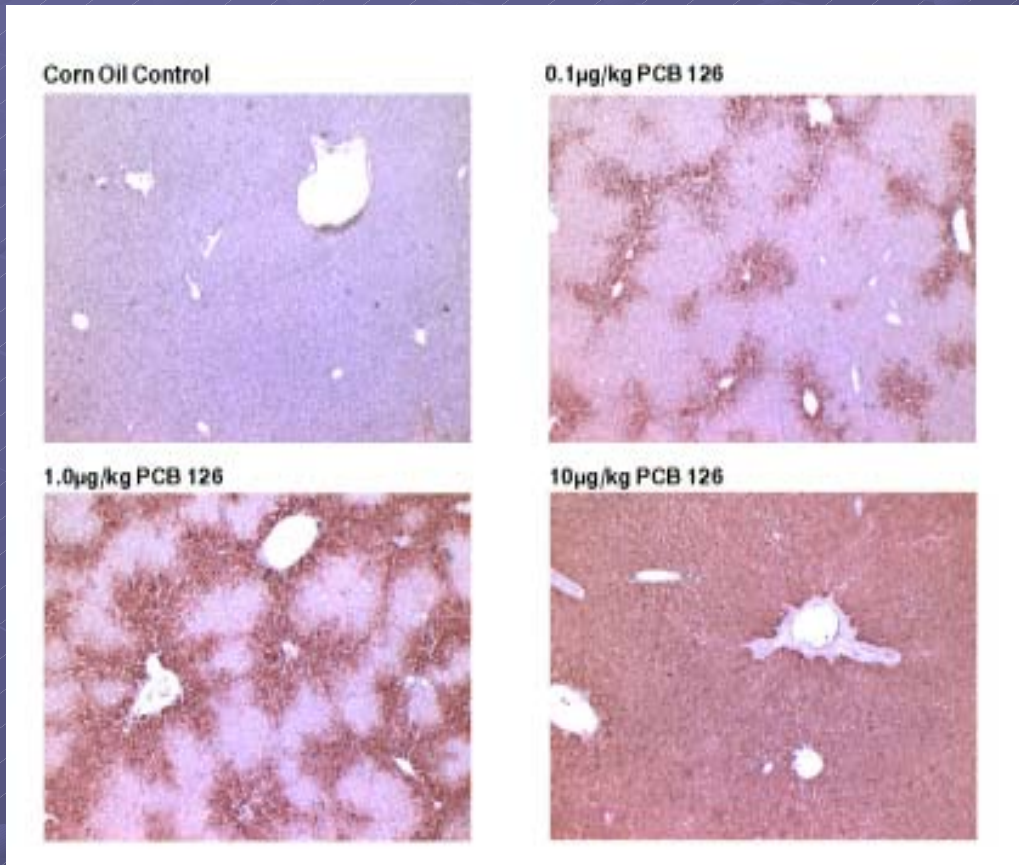
Binary and Graded Responses in Gene Networks



Most responses are binary (either/or) rather than graded!

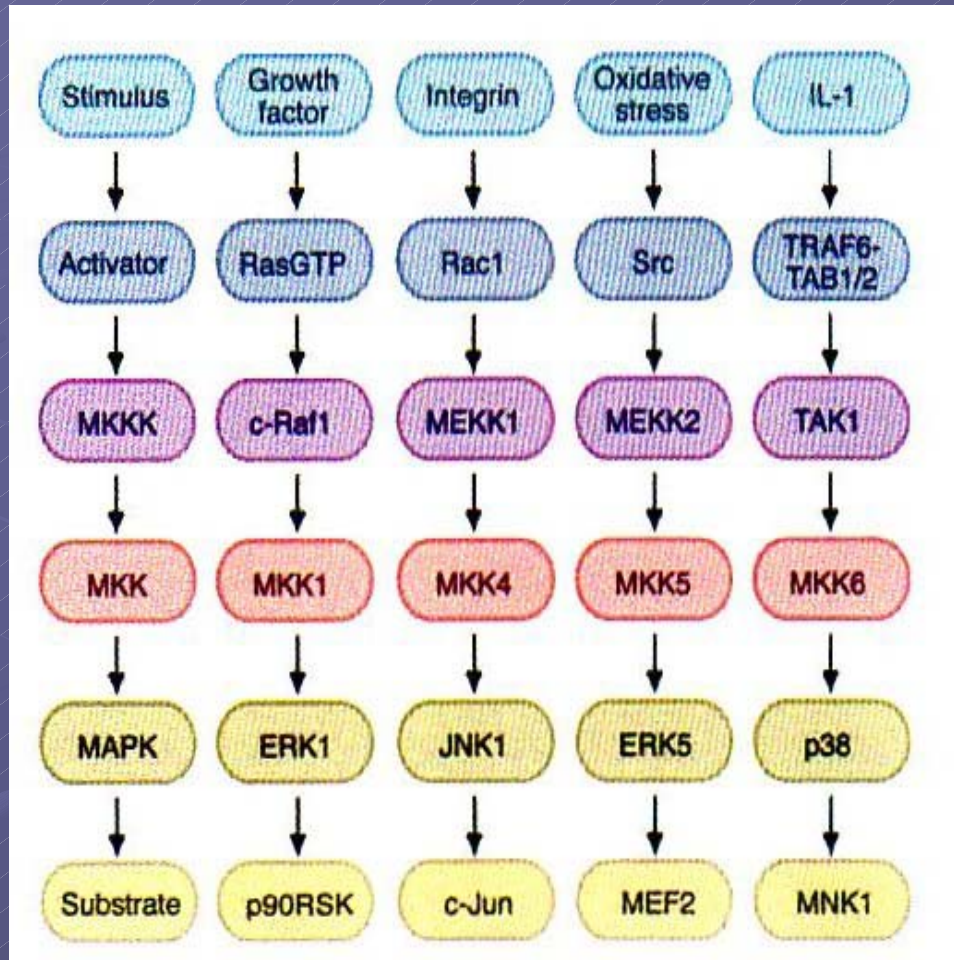
Louis and Becskei, STKE, 30 July 2002.

Cell Activation by Xenobiotics has Switch-Like Characteristics



Induction is related to activation of the Aryl Hydrocarbon (Ah) receptor by PCB 126, leading to a coordinated response of a battery of genes. The pattern of induction indicates a 'switch' moving the cell abruptly between two different phenotypes.

Mitogen Activated Protein Kinases

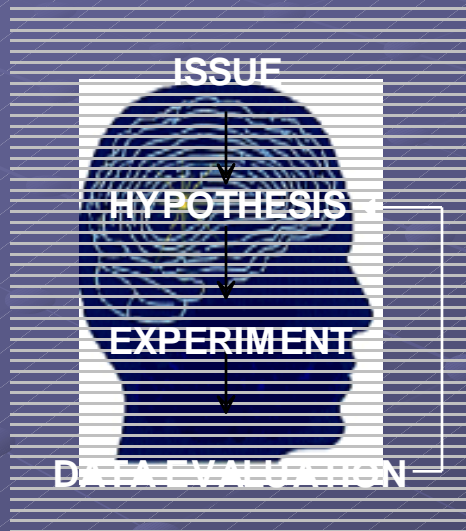


Several families of MAP kinase families act as phosphorylation cascades in controlling a wide variety of biological processes.

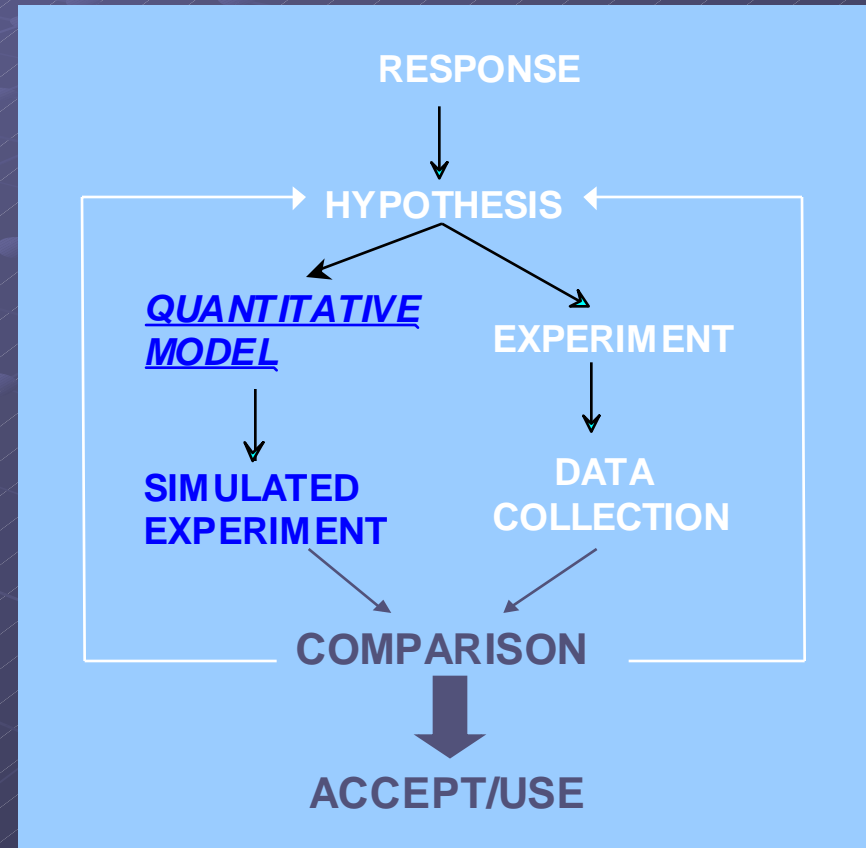
Oxidative stress
DNA repair
Cell Cycle
G-Protein-Responses
NR responses

Johnson, G.L. and Lapadat, R. (2002). Mitogen-Activated Protein Kinase Pathways Mediated by ERK, JNK, and P38 Protein Kinases. Science, 298, 1911-1912.

Computational Biology

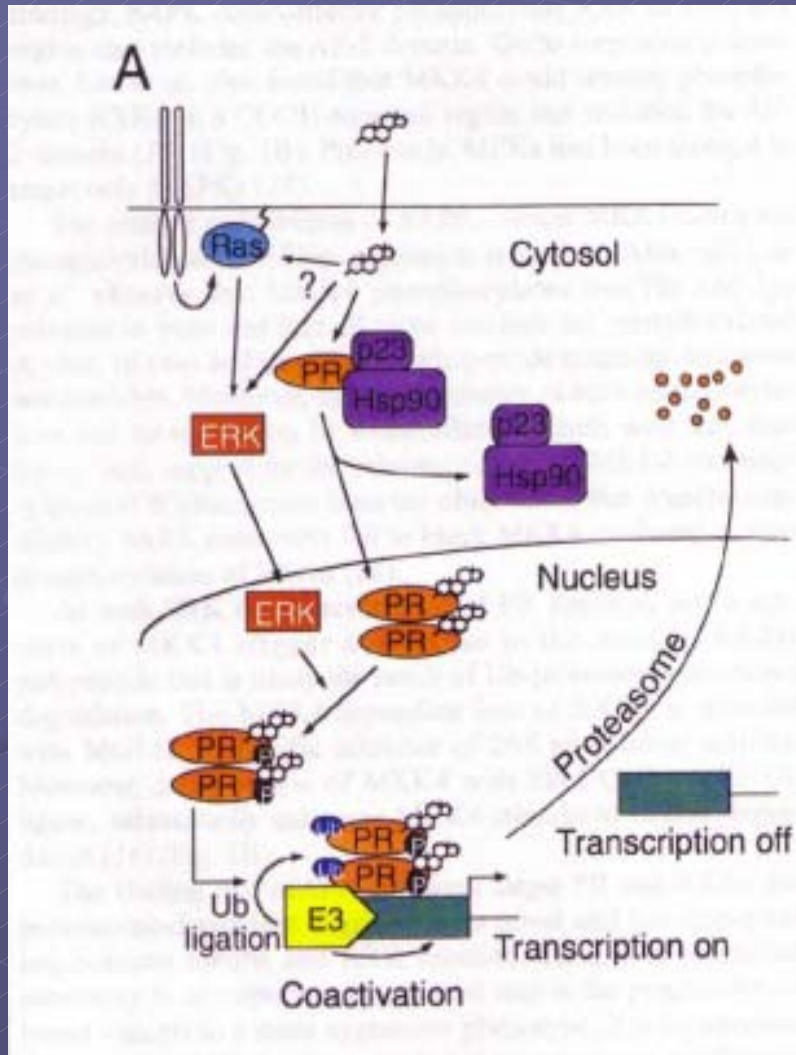


(Intuitive modeling)



(Formal + intuitive modeling)

MAP Kinases and the Regulation of Nuclear Receptors



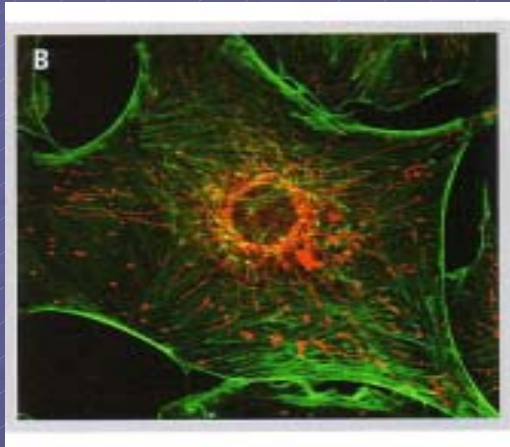
Nuclear receptors work through genomic and non-genomic pathways to activate expression of groups of genes. The two pathways are usually both involved.

Kyriakis, STKE, 5 September 2000.

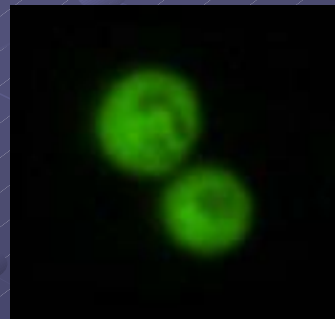
Computational Biology, Biological Networks & Risk Assessments

- Computational models, describing hypothesized molecular circuits quantitatively, allowing hypothesis testing and dose-response assessments
- Imaging methods applied to fluorescently labeled proteins and partnering proteins with kinetic analysis in 'normal' and knock-down cells to test, refine hypotheses

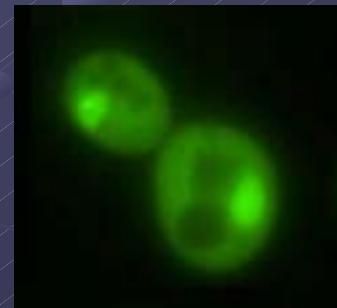
Protein Networks in Cells – Functional Proteomics



Increasing use of labeled proteins and microscopic imaging in fixed and for localization and kinetics in live, single cells



+ ligand
→

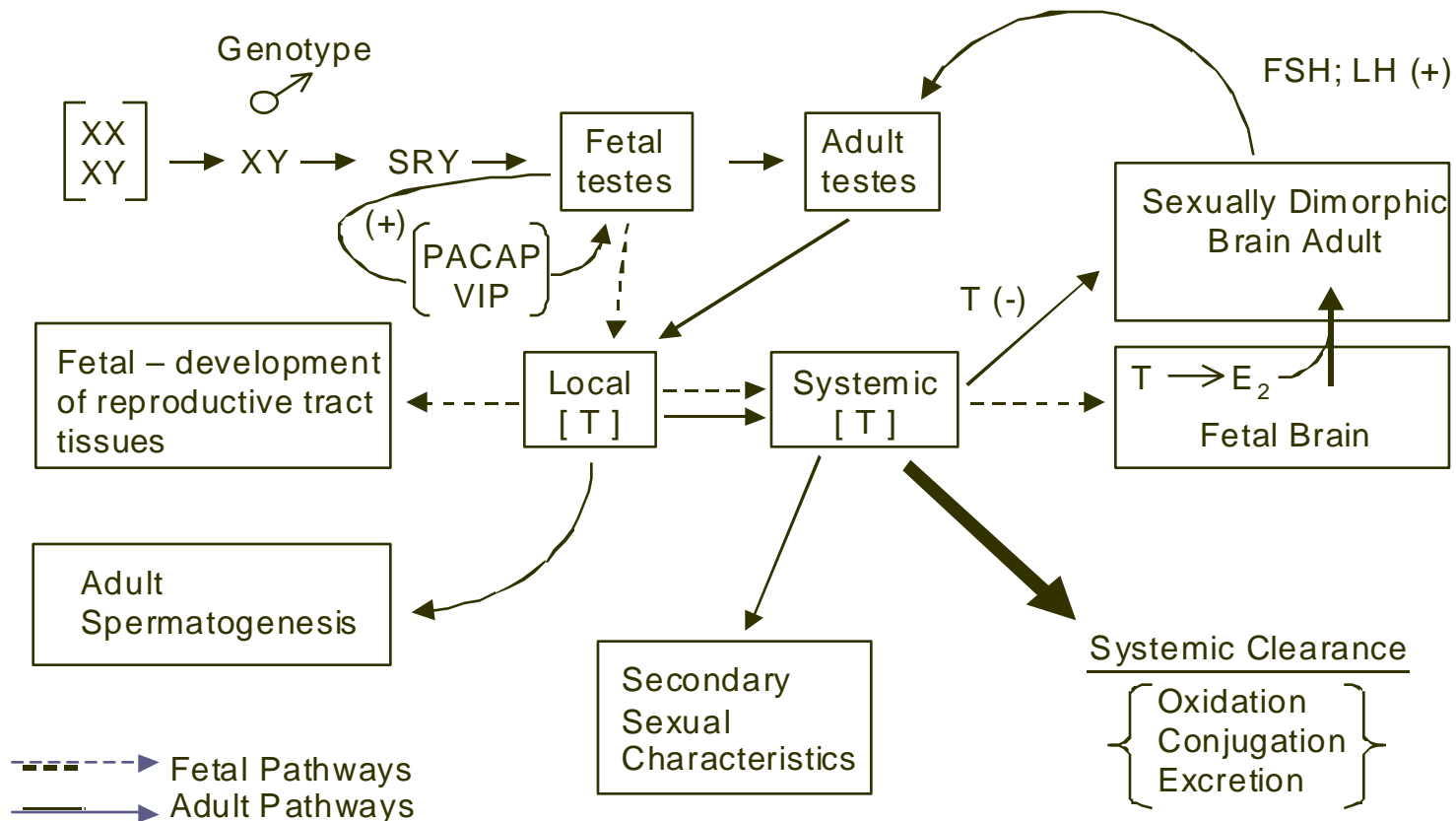


Nuclear Receptor-GFP

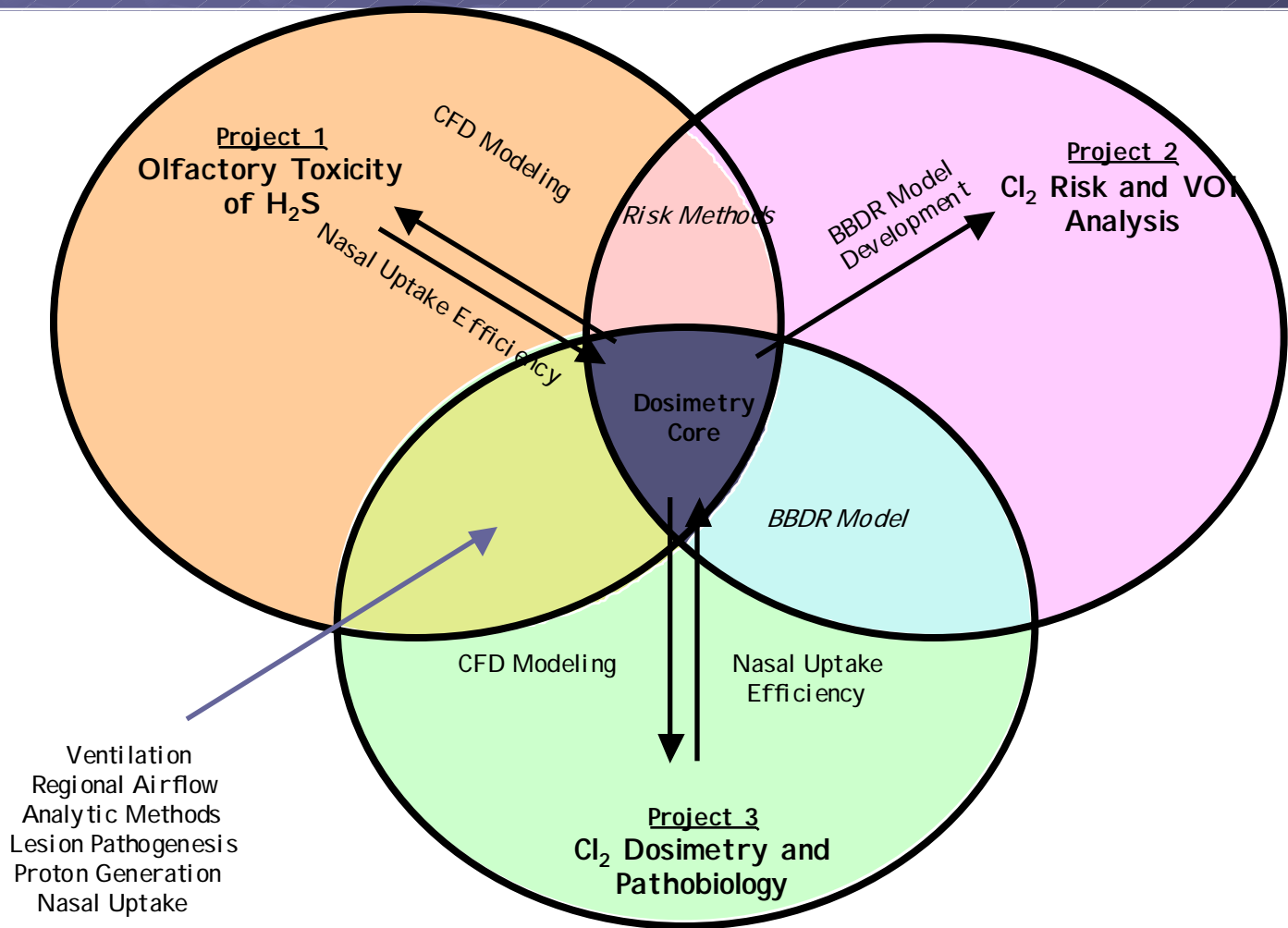
Translocation

Male Reproductive Tract Development

Organizational and Functional Responses to Testosterone



Respiratory Tract Responses: Systems Biology and Dosimetry



Systems Biology in Environmental Health Research

- Focus shifts from toxicity as a fundamental property to a more quantitative descriptions of normal biology and physiology.
- Chemical exposures cause perturbation; some perturbations are large enough to cause adverse responses and some are so small as to be without significant consequences.
- Positioned to pursue these approaches in our core research areas related to reducing uncertainties in risk assessment

The Rewards:

- Better linkage between experiments and quantitative hypotheses testing (efficiency)
- Focus on normal biology, perturbations and health consequences rather than high dose hazards
- Coupled dosimetry & BBDR models to support risk assessments, reducing risk uncertainties